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A FACILE SYNTHESIS OF 7,10-DIDEOXY TAXOL AND 7-EPI-10-DEOXY TAXOL

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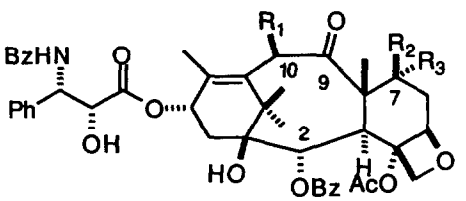
Abstract: *7,10-Dideoxy taxol 2 was prepared from baccatin III in 4 steps via the Barton deoxygenation reaction. Similarly, 7-epi-10-deoxy taxol 3 was prepared in one step from 7-epi taxol in high yield. The key reaction was the tributyltin hydride- mediated direct reduction of the C_{10} acetate.*

Taxol (**1**)™, a structurally unique diterpenoid, was isolated from the western yew *Taxus brevifolia* by Wani and Wall in 1971.[1] It was recently approved for the treatment of ovarian cancer and present studies involving breast, colon, and lung cancers have shown promising results.[2,3]



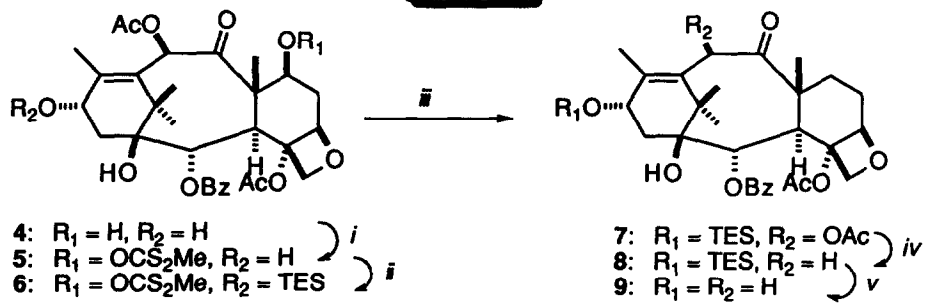
1: R_1 = OAc, R_2 = OH, R_3 = H
TAXOL
2: $R_1 = R_2 = R_3$ = H
7,10-DIDEOXY TAXOL
3: $R_1 = R_2$ = H, R_3 = OH
7-EPI-10-DEOXY TAXOL

Owing to the encouraging clinical results, taxol (**1**) has been the target of several structure-activity studies.[4] In previous reports, we have shown that the benzoate moiety at C_2 is essential for its biological activity,[5] while the acetate functional group at C_{10}, on another hand, contributes very little to receptor binding.[6] Similarly, the hydroxyl group at C_7 is not involved in binding.[7] In this communication we wish to report the development of an extremely concise and effective approach to 10-deoxy taxanes, exemplified by 7,10-dideoxytaxol (**2**), and 7-epi-10-deoxy taxol (**3**).

Our synthesis of compound **2** began with xanthate **5** (Scheme 1), which was prepared from baccatin by treatment of a solution of **4** in tetrahydrofuran and carbon disulfide with sodium hydride and iodomethane. We found that silylation at C-13 was necessary in order to improve solubility, and for the deoxygenation studies we used xanthate **6**. In our early studies we had found that treatment of xanthate **6** with five equivalents of Bu_3SnH in benzene at 80°C yielded the corresponding 7-deoxy derivative (**7**).[7] However,we were surprised to observe that under slightly different conditions (10 equiv Bu_3SnH, toluene, 100°C, 12 h), 7,10-dideoxy baccatin (**9**) was produced in high yield. Furthermore, treatment of 7-deoxy derivative (**7**) with six equivalent of Bu_3SnH (100°C in toluene) afforded 7,10-dideoxy baccatin derivative (**8**) in 90% yield. These results have led us to conclude that, after reduction at C-7, deoxygenation at C-10 can be readily effected under typical Barton conditions. This

observation is precedented by reports describing the reductive cleavage of certain activated (*e.g.* allylic, α-keto) benzoates .[8]

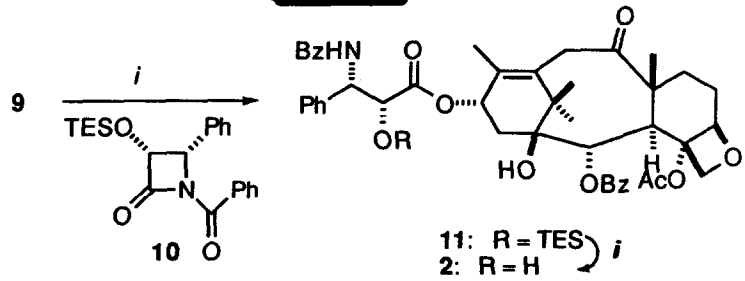
Scheme 1



Reagents and conditions:(i) NaH/THF/CS_2, then MeI (57%); (ii) TESCl/imidazole/DMF (86%); (iii) **5** to **9** Bu_3SnH/AIBN/PhMe/100°C (85%); (iv) **7** to **8** Bu_3SnH/AIBN/PhMe/100°C (90%); (v) TBAF/THF (76%)

With 7,10-dideoxy baccatin (**9**) in hand, side chain attachment reaction via Holton's methodology,[9] using chiral β-lactam (**10**) as the side chain source,[10] was performed. The desired 7,10-dideoxy taxol (**2**) was obtained after desilylation of compound **11**. (Scheme 2) *Thus, an efficient four-step synthesis of 7,10-dideoxy taxol was accomplished.*[7]

Scheme 2

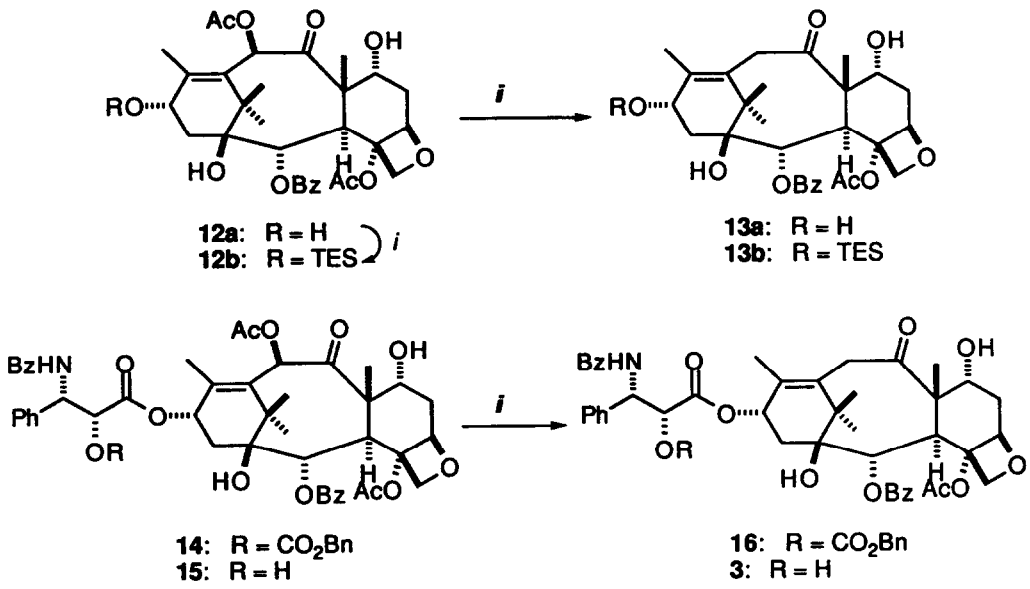


Reagents and conditions: (i) LiHMDS/THF/**10** (36%); (ii) TBAF/THF (66%)

We then continued to examine the scope of this tributyltin radical-mediated direct C_{10} reduction reaction and found that this reaction can be extended to C_7-epi baccatin and taxol derivatives. As can be seen from Scheme 3, C_{10}-deoxy baccatin **13a,b** were prepared from their corresponding 7-epi baccatin **12a,b** in good yield. When taxol derivative **14**[11] was chosen as starting material, we were delighted to find that 10-deoxy compound (**16**) was produced cleanly. *Similarly, 10-deoxy-7-epi taxol (3) was obtained in excellent yield from 7-epi taxol*[11] *(15) in one step.* However, treatment of taxol and baccatin derivatives under similar conditions led to a mixture of products.[12] Surprisingly, 7-triethylsilyl taxol did not undergo the deoxygenation reaction under our typical conditions. This observation suggests that the reductive process is initiated by attack of the tributyltin radical onto the oxygen of the C9 carbonyl, and that bulky groups in the vicinity of C9 sterically

hinder the approach of tin radicals to the carbonyl oxygen.

Scheme 3



Reagents and conditions: (i)TESCl/imidazole/DMF (83%); (ii) Bu_3SnH/AIBN/PhMe/100°C **13a** (76%); **13b** (85%); **16** (82%); **3** (88%)

This new deoxygenation chemistry provides direct and efficient access to 7,10-dideoxytaxol,[7] and constitutes a potentially general and rapid approach to other 10-deoxytaxanes. As predicted on the basis of our previous SAR work, [6,7] compound **3** displayed potent biological activity.[13,14]

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References and Notes

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3 Taxol is registered trademark of Bristol-Myers Squibb Company.

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11 C_7-epi taxol (**15**) was prepared by treatment of taxol with two equivalents of DBU in toluene at 90°C for 40 min. 2'Cbz-7-epi taxol (**14**) was prepared by treatment of **15** with benzyl chloroformate (3 eq) and diisopropylethylamine (3 eq) in dichloromethane at 0°C.

12 Treatment of taxol **1** with Bu_3SnH/AIBN (100°C in toluene) yielded 10-deoxy-7-epi taxol (39%) and 7-epi taxol (16%) together with 23% of the starting material. Likewise, treatment of baccatin **4** with same reagent under identical conditions gave 10-deoxy-7epi baccatin (10%) and 7-epi baccatin (5%), together with 62% of the starting material.

13 Cytotoxicity in a sensitive human colon carcinoma line (HCT-116) was as follows: IC_{50} taxol, 0.004 μM; compound **3**, 0.004 μM.

14 All new compounds gave satisfactory ^{13}C- and ^{1}H-NMR spectra and accurate mass determinations.

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